

1/18

E16



FIG. 1A

P60

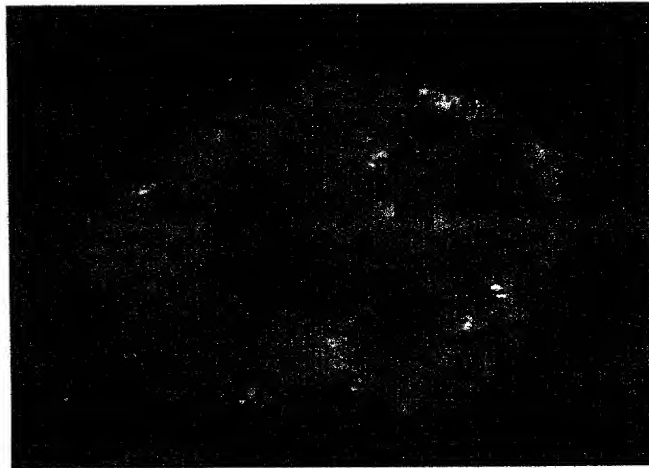


FIG. 1B



← 1018 bp

← 507 bp

FORWARD PRIMER [GCGGGGCGGTGCGTGACTAC]
REVERSE PRIMER [GGGTGGTGAGGGTTGAGGTTTGTG]

FIG. 2

NESTIN POSITIVE CELLS PROLIFERATE AROUND ISLETS IN VITRO



FIG. 3

3/18

100x

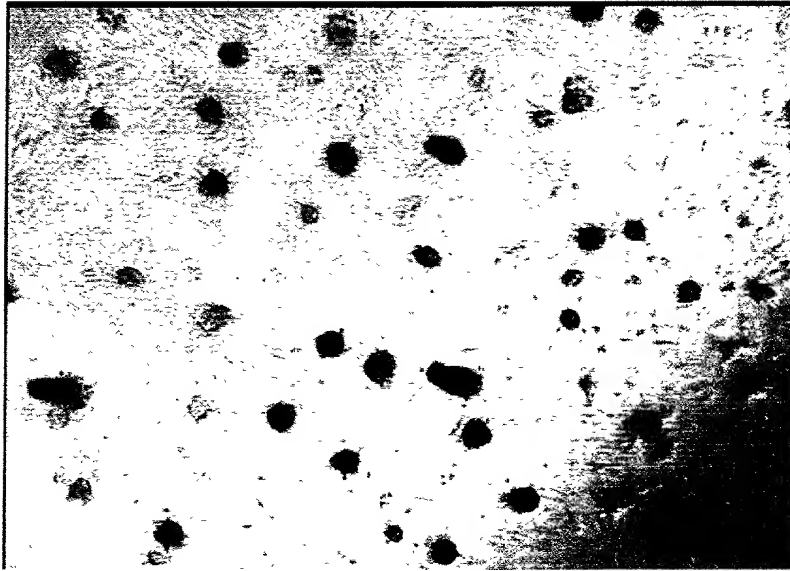


FIG. 4A

200x

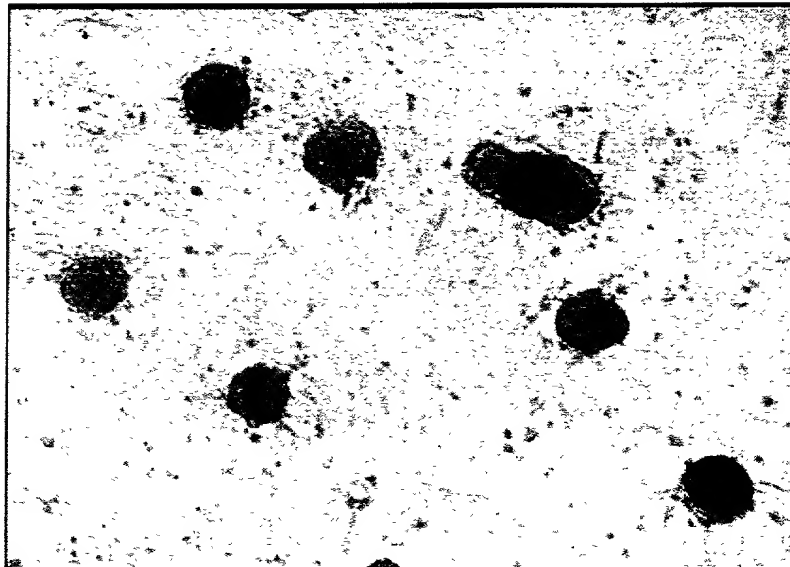


FIG. 4B

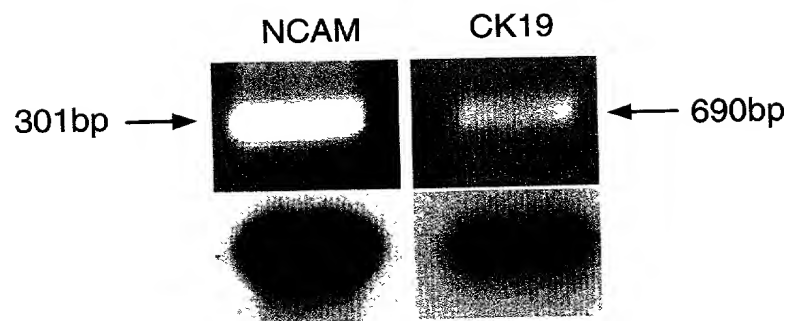


FIG. 5

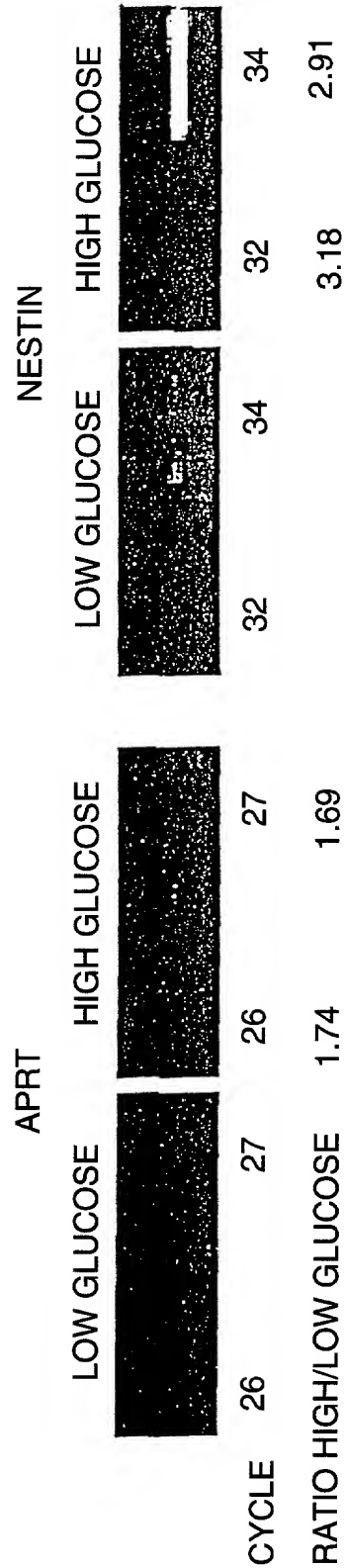


FIG. 6

Nestin Amino Acid Sequence:

"MEGCMGEESFQMWELNRRLEAYLGRVKALEEQNELLASAGLGGLR
 RQSADTSWRAHADDELAALRALVDQRWREKHAAEVARDNLAELEGVAGRCEQLRL
 ARERTTEEVARNRRAVEAEKCARAWLSSQGAELERELEALRVAHEEERVGLNAQAAC
 APRLPAPPRPPAPAPEVEELARRLGEAWRGAVRGYQERVAHMETSLDQTRERLARAVQ
 GAR
 EVRLELQQLQAERGGLLERRAALEQRLEGRWQERLRATEKFQLAVEALEQEKQGLQSQ
 IAQVLEGRQQLAHLKMSLSLEVATYRTLLEAENSRLQTPGGGSKTSLSFQDPKLELQF
 PRTPEGRRLGSLLPVLSPTSLPSPLPATLETPVPAFLKNQEFLQARTPTLASTPIPT
 PQAPSPAVDAEIRAQDAPLSLLQTQGGRKQAPEPLRAEARVAIPASVLPGPPEPGGQR
 QEASTGQSPEDHASLAPPLSPDHSSLEAKDGESGGSRVFSICRGEQEGQIWGLVEKET
 AIEGKVVSLLQQEIWEEEDLNRKEIQDSQVPLEKETLKS LGEEIQESLKTLENQSHET
 LERENQECPRSLEEDLETLSLEKENKRAIKGCGGSETSRKRGCRLKPTGKEDTQTL
 QSLQKENQELMKSLEGNLETFLFPGTENQELVSSLQENLESLETALEKENQEPLRSPEV
 GDEEALRPLTKENQEPLRSLEDENKEAFRSLEKENQEPLKTLLEEDQSIVRPLETENH
 KSLRSLEEQDQETLRTLEKETQQRRLSLGEQDQMTLRPPEKVDLEPLKSLDQEIARPL
 ENENQEFLKSLKEESVEAVKSLETEILESLSAGQENLETLSKETQAPLWTPPEINK
 SGGNESSRKGNSTTGVCSEPRDIQTPGRGESGHIISGSMEPGEFEISRGVDKESQ
 RNLEEEENLGKGEYQESLRSLEEEGQELPQSADVQRWEDTVEKDQELAQESPPGMAGV
 ENKDEAELNLREQDGTGKEEVVEQELNATEEVWFPGEHPENPEPKEQRGLVEGAS
 VKGGAEGLDPEGQSQQVGTPLQAPQGLPEAIEPLVEDDVAPGGDQASPEVMLGSEP
 AMGESAAGAEPGLGQGVGGLGDPGHLTREEVMEPPLEESLEAKRVQGLEGPRKDLLE
 AGGLGTEFSELPGKSRDPWEPPREGREESEAEAPRGAEAEAFPAETLGHTGSDAPSPWP
 LGSEEAEDVPPVLVSPSTYTPILEDAPGLQPQAEQSQEASWGVQGRAEAGKVESEQ
 EELGSGEIPGLQEEGESREESEDELGETLPDSTPLGFYLRSPSPRWTPLESRGH
 PLKETGKEGWDPAVLASEGLEEPSEKEEGEEGEEECGRDSDLSEEFEDLGTEAPFLPG
 VPGEVAEPLGQVPQLLLDPAAWDRDGESDGFADDEESGEEGEEDQEEGREPGAGRWP
 GSSVGLSLQALSSSQRGFLESDSVSVSPWDDSLRGAVAGAPKTALETESQDSAEP
 SEEESDPVSLEREDKVPGPLEIPSGMEDAGPGADIIGVNGQGNLEGKSQHVNGGVMN
 GLEQSEESGARNALVSEGDRGSPFQEEEGSALKRSSAGAPVHLGQGQFLKFTQREGDR
 ESWSSGED"

Nestin Nucleotide Sequence:

BASE COUNT 1238 a 1176 c 1676 g 764 t ORIGIN 1

atggagggct gcatggggga ggagtcgttt cagatgtggg agctcaatcg ggccttgag 61
 gcctacctgg gccgggtcaa ggcgttgag gacgagaatg agctgctcag cgccggactc 121
 ggggggctcc ggcgacaatc cgcgacacc tcctggcggg cgcagccga cgacgagctg 181
 gcggccctgc gtgcgctcgt tgaccaacgc tggcgggaga agcacgcggc cgaggtggcg 241
 cgcgacaacc tggctgaaga gctggagggc gtggcaggcc gatcgagca gctgcggctg 301
 gcccgggagc ggacgacgga ggaggtagcc cgcaaccggc ggcggctga ggcagagaaa
 361 tgcgcccggg cctggctgag tagccagggg gcagagctgg agcgcgagct agaggctcta
 421 cgcgtggcgc acgaggagga ggcgctcggg ctgaacgcgc aggctgcctg tgccccccgc

FIG. 7A

481 ctgcccgcgc cgccccggcc tcccgcgcgc gccccggagg tagaggagct ggcaaggcga
 541 ctgggcgagg cgtggcgcg ggcaagtgcgc ggctaccagg agcgcgtggc acacatggag
 601 acgtcgctgg accagaccgc cgagcgctg gcccgggcgg tgcagggtgc ccgcgaggtc
 661 cgcttgagc tgcagcagct ccaggctgag cgcggaggcc tcttgagcg cagggcagcg
 721 ttggaacaga ggttgagggg ccgctggcag gagcggctgc gggctactga aaagtccag
 781 ctggctgtgg aggcctgga gcaggagaaa cagggcctac agagccagat cgctcaggtc
 841 ctggaaggtc ggcagcagct ggcgacctc aagatgtccc tcagcctgga ggtggccacg
 901 tacaggaccc tcttgagggc tgagaactcc cggctgcaa cacctggcgg tggctccaag
 961 acttccctca gcttcagga cccaagctg gagctgcaat tccctaggac ccagagggc
 1021 cggcgtcttg gatcttgct ccagctctg agcccaactt cctccctc accctgcct
 1081 gctacccttg agacacctgt gccagcctt ctaagaacc aagaattcct ccaggcccgt
 1141 acccctacct tggccagcac cccatcccc ccacacctc aggcacctc tctgtctga
 1201 gatgcagaga tcagagccca gcatgctct ctctctgc tccagacaca ggtgggagg
 1261 aacaggctc cagagccctc gcggtctgaa gccagggtg ccattcctgc cagcgtctg
 1321 cctggaccag aggagcctgg gggccagcgg caagaggcca gtacaggcca
 gtccccagag 1381 gaccatgcct cctggcacc accctcagc cctgaccact ccagtttaga
 ggctaaggat 1441 ggagaatccg gtgggtctag agtgttcagc atatccgag gggaaggatga
 agggcaaatc 1501 tgggggttg tagagaaaga aacagccata gagggcaaag tgtaagcag
 ctgacagcag 1561 gaaatatggg aagaagagga tctaacagg aaggaaatcc aggactcca
 ggttccttg 1621 gaaaaagaaa cctgaagtc tctgggagag gagattcaag agtcactgaa
 gactctgga 1681 aaccagagcc atgagacact agaaaggag aatcaagaat gtccgaggtc
 tttagaaga 1741 gacttagaaa cactaaaaag tctagaaaag gaaaataaa gagctattaa
 aggatgtgga 1801 ggtagtgaga cctctagaaa aagaggctgt aggcaactta agcctacagg
 aaaagaggac 1861 acacagacat tgcaatccct gcaaaaggag aatcaagaac taatgaaatc
 tctgaaggt 1921 aatctagaga cattttatt tccaggaacg gaaatcaag aattagtaag
 ttctctgaa 1981 gagaacttag agtcattgac agctctgga aaggagaatc aagagccact
 gagatctcca 2041 gaagtgggg atgaggaggc actgagacct ctgacaaagg agaactcagga
 acccctgagg 2101 tctctgaag atgagaaca agaggcctt agatctctag aaaaagagaa
 ccaggagcca 2161 ctgaagactc tagaagaaga ggaccagagt attgtgagac ctctagaaac
 agagaatcac 2221 aatcactga ggtctttaga agaacaggac caagagacat tgagaactct
 tgaaaaagag 2281 actcaacagc gacggaggtc tctaggggaa caggatcaga tgacattaag
 acccccagaa 2341 aaagtggatc tagaaccact gaagtctct gaccaggaga tagctagacc
 tcttgaatat 2401 gagaatcaag agttcttaa gtcactcaa gaagagagcg tagaggcagt
 aaaatcttta 2461 gaaacagaga tctagaatc actgaagtct gcgggacaag agaacctgga
 aacactgaaa 2521 tctccagaaa ctcaagcacc actgtggact ccagaagaaa taaataaatc
 agggggcaat 2581 gaatctcta gaaaaggaaa tcaagaacc actggagtct gtggaagtga
 accaagagac 2641 attcagactc ctggaaggag agaactcagga atcattgaga tctctgggag
 catggaacct 2701 ggagaatttg agatctccag aggagtagac aaggaaagtc aaaggaatc
 ggaagaggaa 2761 gagaacctgg gaaagggaga gtaccaagag tactgaggt ctctggagga
 ggagggacag 2821 gagctgccgc agtctgcaga tgtgcagagg tgggaagata cgggtggagaa
 ggaccaagaa 2881 ctggctcagg aaagccctcc tgggatggct ggagtggaaa ataaggatga
 ggcagagctg 2941 aatctaaggg agcaggatgg cttcactggg aaggaggagg tggtagagca
 gggagagctg 3001 aatgccacag aggaggtctg gttccaggc gaggggcacc

FIG. 7B

cagagaaccc tgagcccaaa 3061 gagcagagag gcctggtga gggagccagt
 gtgaaggagg gggctgaggg cctccaggac 3121 cctgaagggc aatcacaaca
 ggtggggacc ccaggcctcc aggtcctcca ggggctgcca 3181 gaggcgatag agcccctggt
 ggaagatgat gtggccccag ggggtgacca agcctcccca 3241 gaggtcatgt tggggtcaga
 gcctgccatg ggtgagtctg ctgcgggagc tgagccaggc 3301 ctggggcagg ggggtggagg
 gctggggggac ccaggccatc tgaccaggga agaggatg 3361 gaaccacccc
 tggaagagga gagtttggag gcaaagaggg ttcagggctt ggaagggcct 3421 agaaaggacc
 tagaggaggc aggtgtctg gggacagagt tctccagct gcctgggaag 3481 agcagagacc
 ctggggagcc tccaggagg ggtaggagg agtcagaggc tgaggcccc 3541
 aggggagcag aggaggcgtt ccctgctgag accctgggcc acactggaag tgatgccct 3601
 tcacctggc ctctggggtc agaggaagct gaggaggatg taccaccagt gctggtctcc 3661
 ccagcccaa cgtacacccc gatcctgga gatgccctg ggctccagcc tcaggctgaa 3721
 gggagtcagg aggttagctg ggggtgagc gggagggtg aagctggga agtagagagc 3781
 gagcaggagg agttgggttc tggggagatc cccgagggcc tccaggagga aggggaggag 3841
 agcagagaag agagcgagga ggatgagctc ggggagacc tccagactc cactcccctg 3901
 ggcttctacc tcaggctccc cacctcccc aggtggacc cactggagag cagaggccac 3961
 cccctcaagg agactgaaa ggagggtg gatcctgctg tcttggtc cgagggcctt 4021
 gaggaacct cagaaaagga ggagggggag gagggagaag aggagtgtg cctgactct
 4081 gacgtgtcag aagaatttga ggacctgggg actgaggcac ctttcttcc tggggtccct
 4141 ggggaggtgg cagaacctct gggccagggtg cccagctgc tactggatcc tgcagcctgg
 4201 gatcgagatg gggagtctga tgggtttgca gataggaag aaagtgggga ggagggagag
 4261 gaggatcagg aggaggggag ggagccagg gctgggcgtt gggggccagg gtcttctgt
 4321 ggcagcctcc aggcctgag tagctccag agagggaat tcttgagtc tgattctgt
 4381 agtgtcagc tccctggga tgacagctt aggggtgag tggctggtc cccaagact
 4441 gccctggaaa cggagtccca ggacagtgt gagccttctg gctcagagga agagtctgac
 4501 cctgttctc tggagaggga ggacaaagtc cctggccctc tagagatccc cagtgggatg
 4561 gaggatgcag gccagggggc agacatcatt ggtgttaat gccaggggcc caacttggag
 4621 gggaagtcac agcatgaaa tgggggagta atgaacgggc tggagcagtc tgaggaaagt
 4681 ggggcaagga atgcgctagt ctctgaggga gaccgaggga gcccttca ggaggaggag
 4741 gggagtgtc tgaagaggtc ttggcagg gctcctgtt accctggcca ggtcagttc
 4801 ctgaagtca ctcagaggga aggagataga gagtctggt cctcagggga ggac //

FIG. 7C

NESTIN/INSULIN

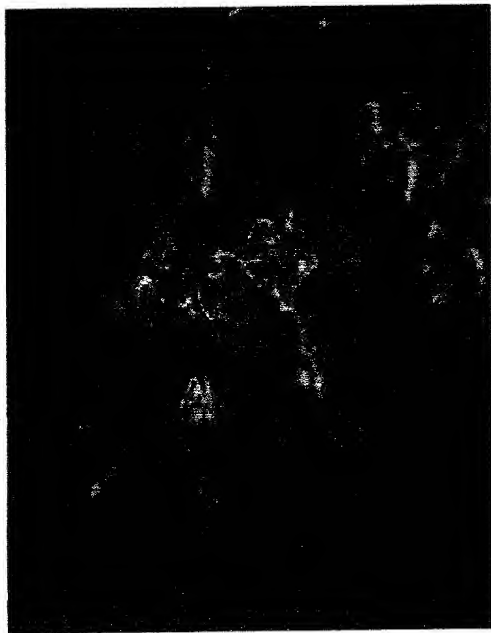


FIG. 8A

E16

NESTIN/INSULIN

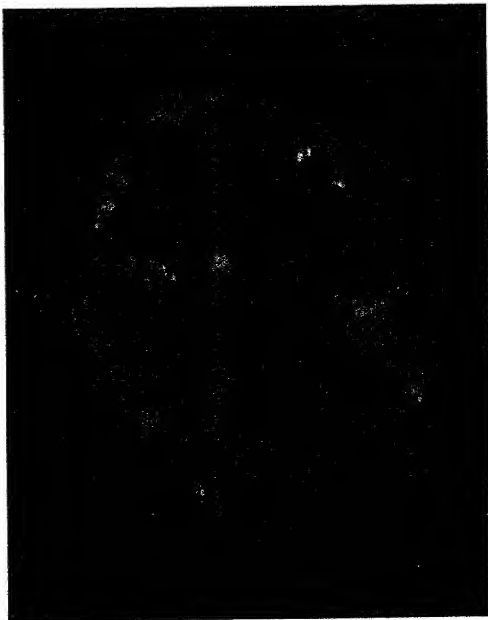


FIG. 8B

P60

NESTIN/COLLAGEN IV



FIG. 8C

P60

NESTIN/NUCLEI

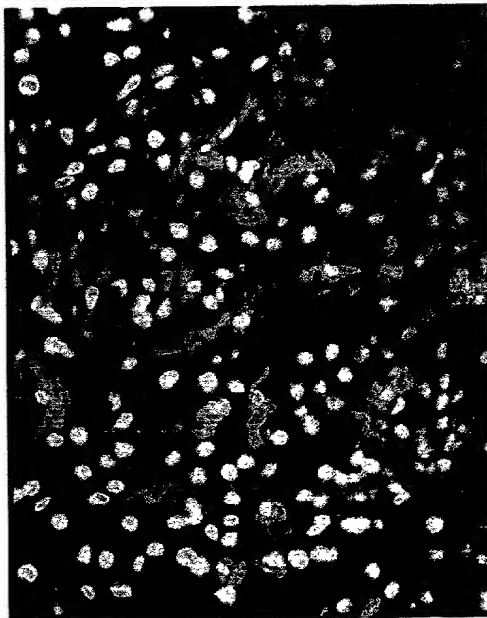


FIG. 8D

P60

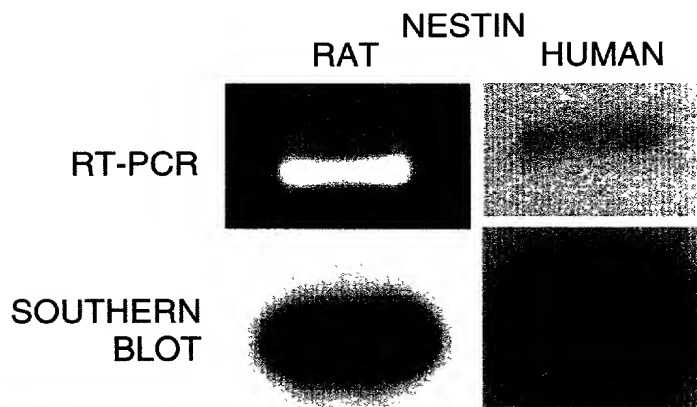


FIG. 8E

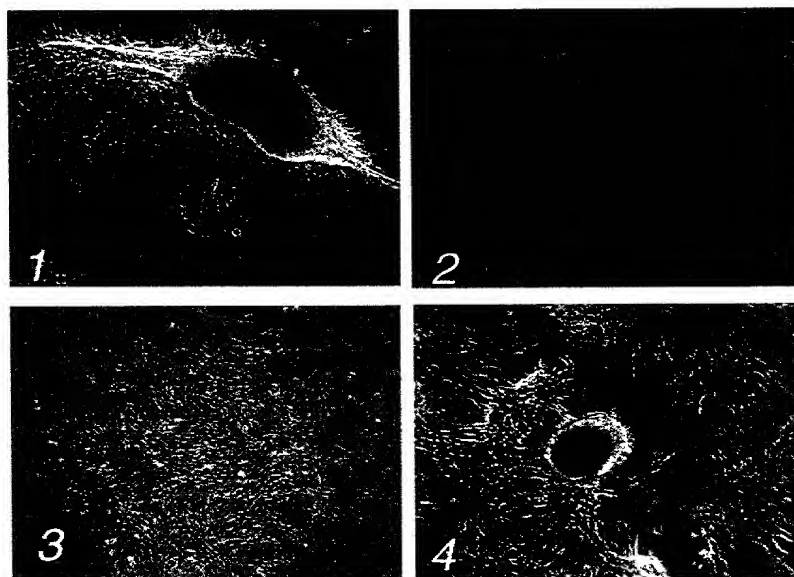


FIG. 9A

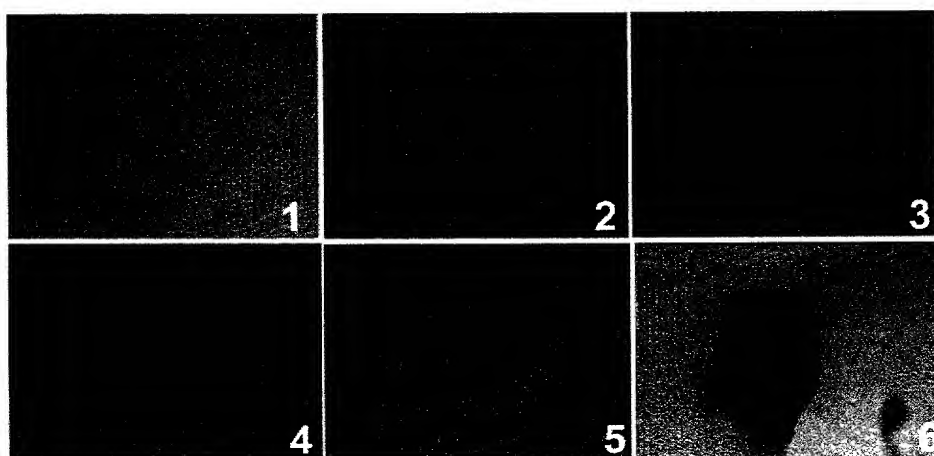


FIG. 9B

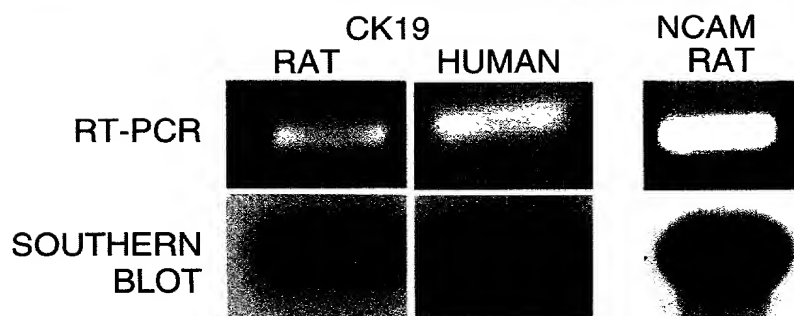


FIG. 9C

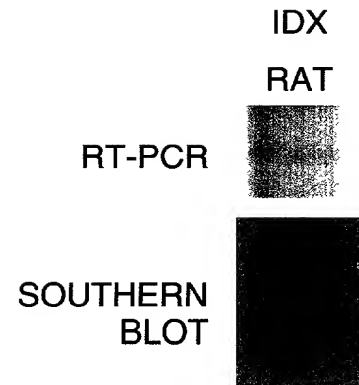
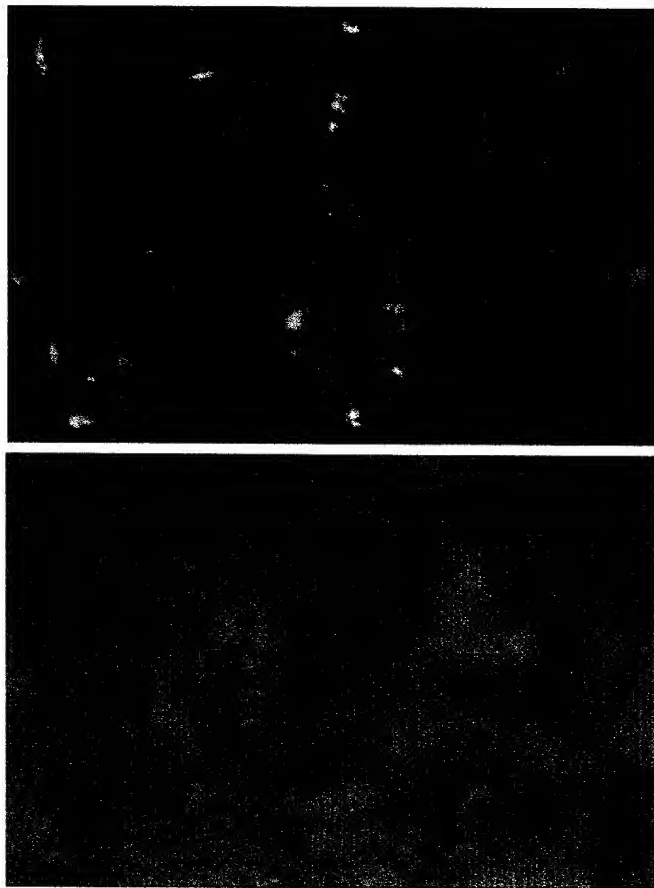


FIG. 10B

FIG. 10A

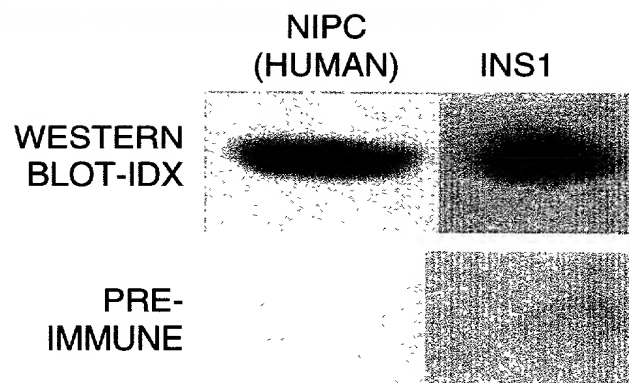


FIG. 10C

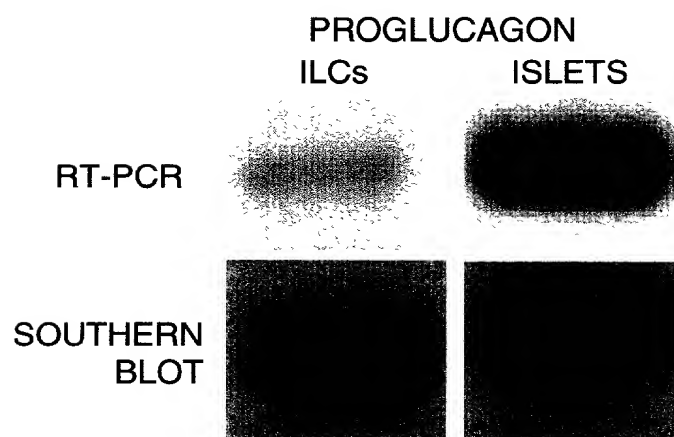
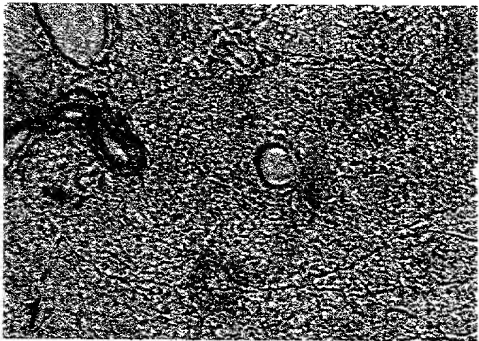


FIG. 10D



CK19 / NESTIN



FIG. 11A

CK19 / NESTIN

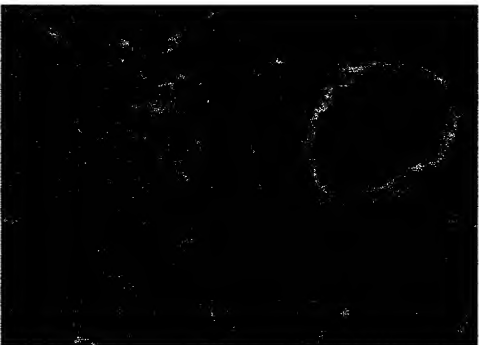
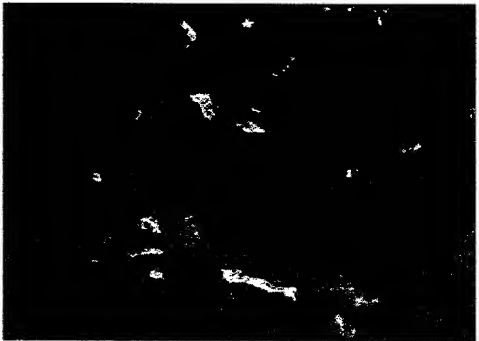


FIG. 11B

NESTIN



NESTIN/NUCLEI

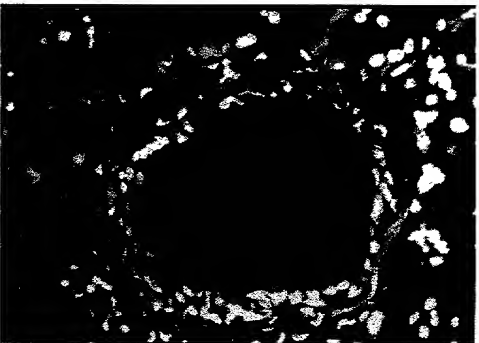


FIG. 11C

FIG. 12 is a schematic diagram of two models of endocrine cell differentiation in a ductal system. Model 1 shows a duct with specialized regions of epithelial cells (indicated by arrows) and an endocrine cell (indicated by an arrow). Model 2 shows a duct with a mesenchymal niche (indicated by an arrow) and an endocrine cell (indicated by an arrow). The duct is composed of epithelial cells (indicated by arrows) and a lumen (indicated by an arrow). The endocrine cell is shown as a specialized cell within the duct.

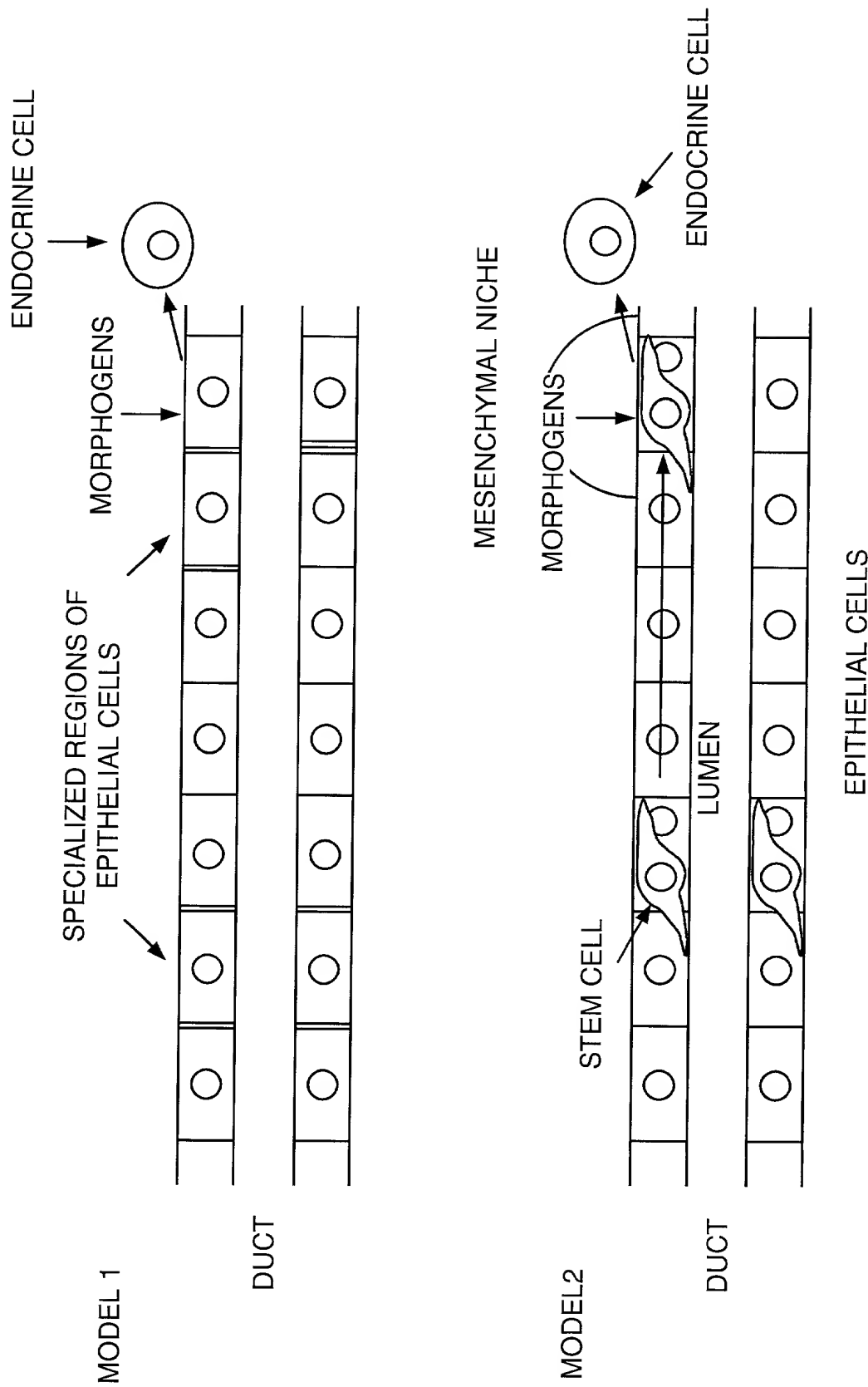


FIG. 12



FIG. 13A



FIG. 13B

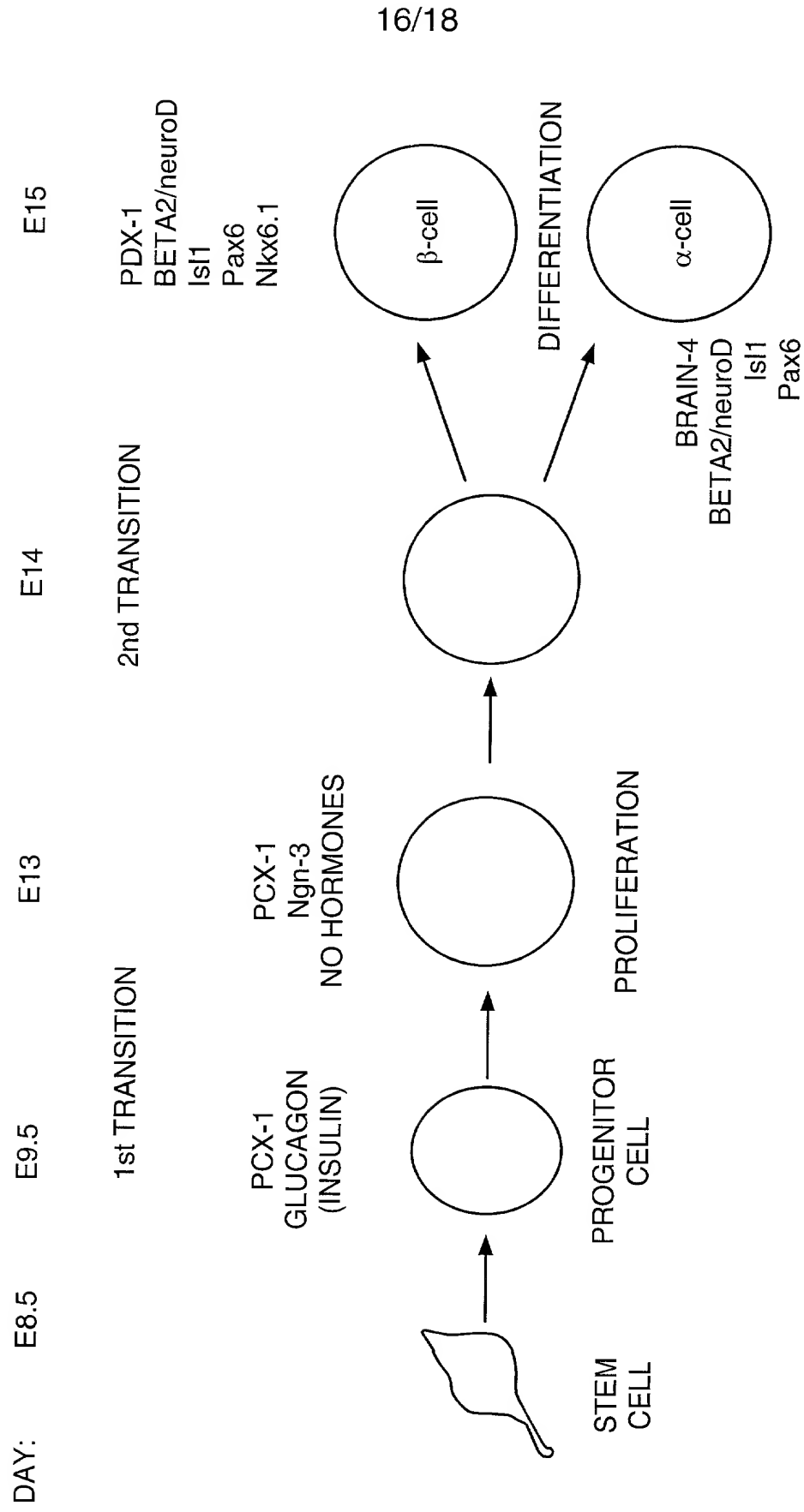


FIG. 14

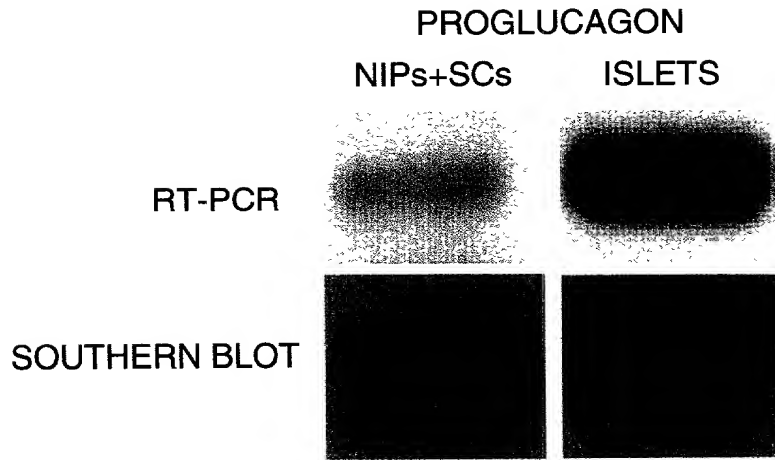


FIG. 15A

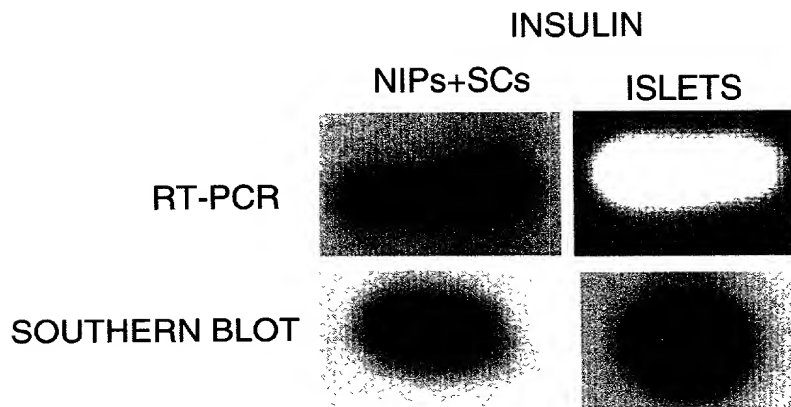


FIG. 15B

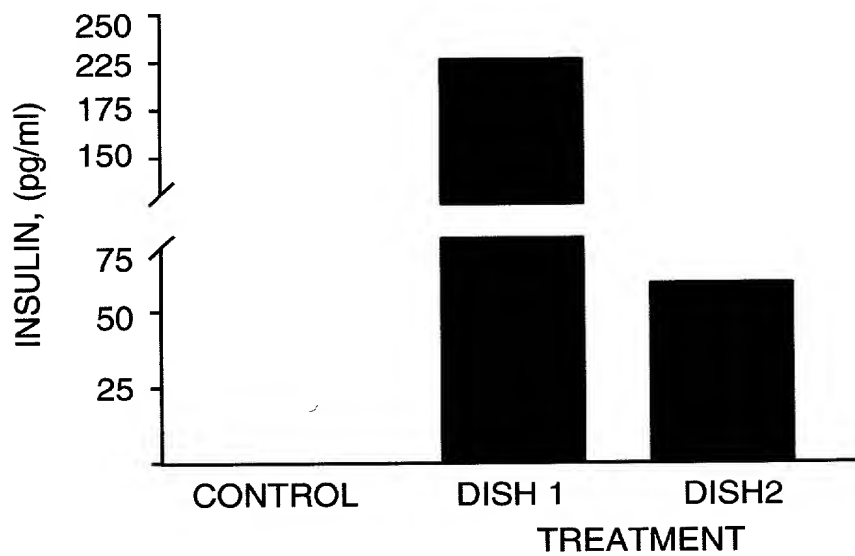


FIG. 15C

NEURO-
ENDOCRINE

SYN



HGFR



GLUT-2



EXOCRINE

AMY



CARB



HEPATIC

TTR



HGF



E-CAD



XBP



AFP



FIG. 16